Effects of Tetrahydrocannabinol on Melatonin Secretion in Man

P. Lissoni, M. Resentini, R. Mauri, D. Esposti*, G. Esposti, D. Rossi, G. Legname and F. Fraschini

Chair of Chemotherapy, and *Institute of Human Physiology, Faculty of Medicine, University of Milan, Milan, Italy

The mechanisms by which tetrahydrocannabiol (Δ^9-THC) affects some neuroendocrine activities have not yet been clarified. Its effects cannot be prevented by pretreatment with α-methyltyrosine, which reduces brain concentrations of norepinephrine and dopamine (*Hollister* 1971). At present, the existence of an endogenous agonist cannot be excluded.

To investigate whether its effects involve the participation of the pineal gland, the response of melatonin (the main pineal hormone), to Δ^9-THC was evaluated in nine agreeing healthy male volunteers, aged between 29 and 33. The substance was administered at 3 p.m. through a 1 g cigarette containing 1% Δ^9-THC. Venous blood samples were drawn from an indwelling catheter in an antecubital vein −20, 0, 20, 60 and 120 mins. after drug administration. According to the same experimental protocol, on the preceding day the test had been performed after smoking one normal cigarette. The whole test was carried out in summer. Sera were separated by centrifugation and stored at −20°C until assayed. Melatonin serum values were measured by means of the RIA method described by *Wetterberg, Erickson, Friberg* and *Vangbo* (1978), using commercially available kits (WHB-Sweden) when the extracts showed melatonin values higher than

detection limit, samples were measured after an adequate dilution. Data were analyzed by Student's t-test and results reported as the mean ± SD.

A very high significant increase (P < 0.001) of melatonin serum mean levels, in comparison to the values observed during saline infusion, was noticed in eight of the nine subjects after Δ^9-THC administration; the highest values were obtained at 120 mins. from administration (Table 1).

In contrast, the last case showed high basal levels of melatonin (289.3 − 321.3 − 157.0 − 72.5 − 181.2 pg/ml, respectively at −20, 0, 20, 60, 120 mins.) without evidence of endocrine or psychiatric disorders, and melatonin peak was significantly inhibited (P < 0.001) by Δ^9-THC, with the lowest levels reached 60 mins. later (304.2 − 311.7 − 294.2 − 306.0 − 314.8 pg/ml respectively at −20, 0, 60, 120 mins.).

These preliminary results are difficult to interpret moreover, at present we are unable to explain the hight melatonin basal level observed in the last case. However, the present data, suggest that Δ^9-THC may regulate the activity of the pineal gland either by stimulating or inhibiting melatonin secretion, and that melatonin response to Δ^9-THC seems to depend upon its basal levels. More-

Table 1 Serum levels (mean values ± SD) of melatonin (pg/ml) in 8 healthy subjects after Δ^9-THC administration.

Times (mins)	−20	0	20	60	120
Δ^9-THC	23.2±2.4	21.3±1.6	87.3±10.4	663.4±88.3	904.1±104.3
Saline	19.8±5.3	20.2±3.4	18.6± 5.7	25.3± 7.1	30.2± 4.8

over, these findings could lead to the hypothesis that the pineal gland is involved in the mechanism of action of Δ^9-THC. However, further research and more data, evaluating melatonin response during different photoperiods of the day and using agonists and antagonists of neurotransmitters, are required to ascertain whether the effects of Δ^9-THC on the pineal gland are direct or mediated.

References

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